April 10, 2013

To Lawmakers:

We are a group of physicians and medical scientists who urge you not to pass without modification the bill HB-1317 or HB-1325, which states that a blood level of 5 ng/mL delta-9-tetrahydrocannabinol (THC) supports a permissible inference of impaired driving.

We are concerned that this law will label as impaired large numbers of medical marijuana patients who are not impaired, yet who may test continuously above 5 ng/mL THC in blood because of long term, high dose cannabis therapy.

Detailed studies in occasional or low dose cannabis users have yielded models that are good at predicting impairment from blood levels in those users. The proposed per se level is based on these studies. For a driver who has used cannabis infrequently or only at low levels, a blood level of 5 ng/mL THC may accurately reflect impairment (A).

In long term and high dose users, THC blood level and impairment do not correlate well at all, and may be wildly different from expected. In one study, blood levels as high as 24 ng/mL occurred in drivers who, according to law enforcement, were not impaired (B).

These results may be surprising, but they can be understood from the clear science around three aspects of THC and cannabinoids:

1. Only a small portion of total THC in blood is active, because most of it is bound to plasma proteins. Like many oily substances, THC binds strongly to proteins in the blood. This binding makes most blood THC inactive. Only the small portion that is dissolved directly in the blood is active THC. When total THC goes up, the percent that is bound goes up also – so a large increase in blood THC level may equate to only a small change in the free, active THC level (C).

Studies that support the per se limit used total THC as the blood measurement – not free, active THC. Yet, it is free THC that relates directly to THC effects. So, it is understandable that studies using only total THC measurements would not accurately identify impaired individuals.

2. THC psychoactivity is blocked by cannabidiol (CBD), which also is found in cannabis. CBD has significant therapeutic effects and is not psychoactive, and is of great interest medically. It is also beneficial that CBD blocks psychoactive effects of THC without blocking therapeutic THC effects like relief of nausea and pain (D).

Adding CBD allows higher THC levels to be used for a greater therapeutic effect without more psychoactivity. So, use of CBD together with THC is another reason that a blood THC level may be above the per se limit, yet not be associated with driving impairment. Availability of high-CBD strains is increasing in Colorado as their benefits become known and more doctors recommend them.

Medical marijuana patients are most likely to use high-CBD cannabis strains, precisely because they can achieve higher blood levels of THC without increased psychoactive side effects. In contrast, occasional or recreational users are far less likely to use or even be aware of these strains.

3. Tolerance to effects of THC readily develops, and psychoactive tolerance occurs more quickly than does tolerance to other effects like pain relief. This means that by slowly increasing their THC dose, patients can reach greater levels of therapeutic relief without greater psychoactivity (E).

With tolerance, a specific blood THC level that causes marked impairment in one person literally causes no impairment in another. This is why a per se limit that does not account for tolerance to THC psychoactive effects in higher dose users cannot distinguish an driver who is impaired from one who is not.

These factors reduce the psychoactive effect of a given THC blood level in long term, high dose users. The exact difference is highly individual. This is why blood THC levels in long term, high dose users correlate poorly with psychoactivity and impairment.

What would an accurate THC blood test for impairment look like? If free, soluble THC in blood were measured, and the value were adjusted for blocking of psychoactivity by CBD, then further adjusted for tolerance, the result might accurately predict impairment even in high dose, long term users.

However, given these well-known factors affecting THC-related impairment, the evidence does not support the inference that 5 ng/mL in blood reflects impairment in high dose, long term users. Instead, we may infer from the evidence that the blood level of a long term, higher dose user indeed will be above 5 ng/mL, regardless of whether the person is actually impaired.

Applying a per se DUI 5 ng/mL limit would be punitive and unfair to patients who, on the recommendation of their doctor, intentionally use cannabis dosing methods that minimize impairment and increase therapeutic benefit, but that may cause high total THC blood levels.

We are concerned that a THC/DUI per se limit will force patients who seek to comply with the law to take dangerous and expensive pharmaceutical medications that do not have nanogram per se limits and are not routinely tested for by the police, but that may have equal or greater potential for impairment as cannabis.

For these reasons, we urge you not to pass HB13-13 as written. Instead, we urge you to add to the bill an exemption from the per se limit for registered medical marijuana patients.

With best regards,

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Supporting Information

A. Key Review of THC Blood Levels in Occasional Users

Chem Biodivers. 2007 Aug;4(8):1770-804. Human cannabinoid pharmacokinetics. Huestis MA. PMID: 17712819.

B. Blood THC Does Not Predict Impairment in Heavy Users.

J Anal Toxicol. 2012 Jul;36(6):405-12. Psychomotor performance, subjective and physiological effects and whole blood Δ9-tetrahydrocannabinol concentrations in heavy, chronic cannabis smokers following acute smoked cannabis. Schwope DM, Bosker WM, Ramaekers JG, Gorelick DA, Huestis MA.PMID: 22589524.

J Psychopharmacol. 2009 May;23(3):266-77. Neurocognitive performance during acute THC intoxication in heavy and occasional cannabis users. Ramaekers JG, Kauert G, Theunissen EL, Toennes SW, Moeller MR. PMID: 18719045.

J Anal Toxicol. 2008 Sep;32(7):470-7. Comparison of cannabinoid pharmacokinetic properties in occasional and heavy users smoking a marijuana or placebo joint. Toennes SW, Ramaekers JG, Theunissen EL, Moeller MR, Kauert GF. PMID: 18713514. "Cannabinoid pharmacokinetics in occasional users is well studied, but the interpretation of data from heavy users is difficult.... The results obtained with occasional users were in contrast to

those of the heavy users.... Of the 12 heavy users, 10 exhibited up to 12.3 microg/L [ng/mL] Delta(9)-tetrahydrocannabinol (THC) prior to smoking."

Traffic Inj Prev. 2006 Jun;7(2):111-6. Relationship between THC concentration in blood and impairment in apprehended drivers. Khiabani HZ, Bramness JG, Bjørneboe A, Mørland J. PMID: 16854704. Suspected drugged drivers in Norway who were judged not to be impaired had THC blood levels as high as 24 ng/mL THC.

C. Protein Binding of Blood THC

IUBMB Life. 2011 Jun;63(6):446-51. Binding of δ9-tetrahydrocannabinol and diazepam to human serum albumin. Fanali G, Cao Y, Ascenzi P, Trezza V, Rubino T, Parolaro D, Fasano M. PMID: 21557446. "THC binds to two different binding sites of human serum albumin... THC binding to the high-affinity site accounts for the low free fraction of the drug in plasma."

Marinol (Dronabinol) Package Insert – Abbott Laboratories: "The plasma protein binding of dronabinol [THC] and its metabolites is approximately 97%."

D. CBD Blocks Psychoactive Effects of THC

Curr Pharm Des. 2012;18(32):4897-905. Potential protective effects of cannabidiol on neuroanatomical alterations in cannabis users and psychosis: a critical review. Hermann D, Schneider M. PMID: 22716143.

Neuropsychopharmacology. 2010 Feb;35(3):764-74. Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Bhattacharyya S, et al. PMID: 19924114.

Br J Pharmacol. 2008 Jan;153(2):199-215. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. Pertwee RG. PMID: 17828291.

Br J Pharmacol. 2007 Mar;150(5):613-23. Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. Thomas A, Baillie GL, Phillips AM, Razdan RK, Ross RA, Pertwee RG. PMID: 17245363.

Med Hypotheses. 2006;66(2):234-46. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. Russo E, Guy GW. PMID: 16209908.

Neuropharmacology. 2004 Dec;47(8):1170-9. Differential effects of THC- or CBD-rich cannabis extracts on working memory in rats. Fadda P, Robinson L, Fratta W, Pertwee RG, Riedel G. PMID: 15567426.

Eur J Pharmacol. 2002 Dec 5;456(1-3):99-106. (-)-Cannabidiol antagonizes cannabinoid receptor agonists and noradrenaline in the mouse vas deferens. Pertwee RG, Ross RA, Craib SJ, Thomas A. PMID: 12450575.

Psychopharmacology (Berl). 1982;76(3):245-50. Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects. Zuardi AW, Shirakawa I, Finkelfarb E, Karniol IG. PMID: 6285406.

Psychopharmacologia. 1974;38(4):329-38. Modification of delta9-THC-actions by cannabinol and cannabidiol in the rat. Fernandes M, Schabarek A, Coper H, Hill R. PMID: 4473791.

Different THC:CBD dosing ratios have different therapeutic effects. GW Pharmaceuticals has patented four THC-CBD combinations for four categories of medical conditions. US Patent 6946150 B2. "Pharmaceutical Formulation". GW Pharma Ltd.

E. Tolerance to THC Effects

Neuropsychopharmacology 2008;33:2505-2016. Blunted psychotomimetic and amnestic effects of delta-9-tetrahydrocannabinol in frequent users of cannabis. D'Souza et al. "These data suggest that frequent users of

cannabis are either inherently blunted in their response to, and/or develop tolerance to the psychotomimetic, perceptual altering, amnestic, endocrine, and other effects of cannabinoids."

AAPS J. 2006 Mar 10;8(1):E112-7. Activation of G-proteins in brain by endogenous and exogenous cannabinoids. Childers SR. PMID: 16584117. "Chronic treatment in vivo with cannabinoids produces significant tolerance to the physiological and behavioral effects of these drugs."

Handb Exp Pharmacol. 2005;(168):691-717. Cannabinoid tolerance and dependence. Lichtman AH, Martin BR. PMID: 16596793.

Eur J Pharmacol. 2005 Mar 7;510(1-2):59-68. Task specificity of cross-tolerance between Delta9-tetrahydrocannabinol and anandamide analogs in mice. Wiley JL, Smith FL, Razdan RK, Dewey WL. PMID: 15740725.

Behav Pharmacol. 2004 Feb;15(1):1-12. Behavioral effects of cannabinoids show differential sensitivity to cannabinoid receptor blockade and tolerance development. De Vry J, Jentzsch KR, Kuhl E, Eckel G. PMID: 15075621.

Crit Rev Neurobiol. 2003;15(2):91-119. Regulation of cannabinoid CB1 receptors in the central nervous system by chronic cannabinoids. Sim-Selley LJ. PMID: 14977366.

J Pharmacol Exp Ther. 2002 Oct;303(1):36-44. Effect of chronic administration of R-(+)-[2,3-Dihydro-5-methyl-3-[(morpholinyl)methyl]pyrrolo[1,2,3-de]-1,4-benzoxazinyl]-(1-naphthalenyl)methanone mesylate (WIN55,212-2) or delta(9)-tetrahydrocannabinol on cannabinoid receptor adaptation in mice. Sim-Selley LJ, Martin BR. PMID: 12235230.

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